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CT-based patient-specific model to predict the risk of hip fracture

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Abstract:

In this review we summarise over 15 years of research and development around the prediction of whole bones strength from Computed Tomography data, with particular reference to the prediction of the risk of hip fracture in osteoporotic patients. We briefly discuss the theoretical background, and then provide a summary of the laboratory and clinical validation of these modelling technologies. We then discuss the three current clinical applications: in clinical research, in in clinical trials, and in clinical practice. On average the strength predicted with finite element models (QCT-FE) based on computed tomography is 7% more accurate that that predicted with areal bone mineral density from Dual X-ray Absorptiometry (DXA-aBMD), the current standard of care, both in term of laboratory validation on cadaver bones and in terms of stratification accuracy on clinical cohorts of fractured and non-fractured women. This improved accuracy makes QCT-FE superior to DXA-aBMD in clinical research and in clinical trials, where the its use can cut in half the number of patients to be enrolled to get the same statistical power. For routine clinical use to decide who to treat with antiresorptive drugs, QCT-FE is more accurate but less cost-effective than DXA-aBMD, at least when the decision is on first line treatment like bisphosphonates. But the ability to predict skeletal strength from medical imaging is now opening a number of other applications, for example in paediatrics and oncology.

KEYWORDS

Compute Tomography; Finite Element Method; Bone and Bones; Biomechanical Strength; In Silico Medicine; In Silico Trials.

INTRODUCTION

The bones forming our skeleton fracture when they are exposed to abnormal loads, or when their biomechanical competence is compromised. 77% of all unintentional injuries that occur annually in the United States are to the musculoskeletal system [1]. In total, 8.9 millions of bone fractures are associated every year to osteoporosis, worldwide [2]. Because the increased propensity to fall and overload, as well as the reduction of biomechanical com- petence of the skeleton are both associated with ageing, projections of prevalence are all quite concerning, because of the ageing population [3].

It is thus very important to develop reliable methods that can estimate the biomechanical strength of specific bones in the skeleton to defined loading conditions, and from those derive the risk of bone fracture associated to the reduced biomechanical competence.

In this review paper we provide a description of the most advanced technologies used for the non-invasive prediction of bone strength, and of the clinical applications that such technologies are finding.

PREDICTING BONE STRENGTH

The intensity of the force required to fracture a human bone, when such bone is loaded in a given direction, is function of three biophysical determinants: the bone geometry, the biomechanical properties of the tissues forming the bone, and the loading condition.

BONE GEOMETRY

While it is possible to estimate the 3D shape of anatomically normal bones from 2D medical images [4], [5], a truly accurate definition of the bone geometry requires 3D medical imaging methods. Historically the first imaging modality used for bone geometry

reconstruction was Computed Tomography (CT) [6]. Today similar accuracy can be obtained using Magnetic Resonance Imaging (MRI) [7]. CT involves the exposure to ionising radiations, whereas MRI does not. However, CT can provide also additional information to build models to predict bone strength, and thus is more commonly used to this purpose. If the CT exam is not already required by the clinical pathway for that disease, a risk-benefit analysis is required in the application to the ethics committee.

Biomechanics properties of bone tissue

Bones are formed by a cellular phase, a non-mineralised extracellular phase, and by a mineralised extracellular phase. There are strong evidences that only the latter contributes to the biomechanical strength of bone; thus, the other phases are neglected, and simply treated as porosities in the mineralised extracellular matrix. Generally speaking, the biomechanical properties of bone (hereinafter the term is used to refer to the mineralised extracellular matrix) depend on the degree of mineralisation, the anatomical location (space), the histological type (osteonal, lamellar, cancellous), and the speed of deformation (time).

The biomechanical deformations of bone vary linearly with the biomechanical stresses up to a deformation of 0.8- 1.0%. In some cases, for example during hip fractures, at that level of deformation a crack propagates macroscopically to fracture in a few milliseconds. In such cases, the prediction of the strength can be done with good accuracy by simply considering the elastic properties of the bone tissue. Vice versa, in some other cases (for example a compression vertebral fracture), bone continues to show significant stiffness even after the deformation exceeds that linearity threshold. In these cases, the behaviour of the bone tissue can be described by knowing the elastic but also the post-elastic properties of the tissue. Here we consider only the first case, for simplicity of exposition, and also because most of the clinical applications we describe in the following sections are based on these linear models.

A first key assumption in the definition of the biomechanical properties of bone tissue is that of spatial scale. Hereinafter we consider models that predict the strength of whole bones, with a spatial resolution in the order of some millimetres. At this scale bone tissue can be assumed to be an heterogenous continuum, whose properties depend only on the degree of mineralisation. The dependence on the anatomical location and the histological type are implicitly considered as they are both function of the apparent mineral density at the continuum scale. Also the dependence on the speed of deformation is considered

implicitly, by correcting the elastic properties with an empirical coefficient, as first proposed in [8].

The mineral content of bone tissue is correlated to the coefficient of x-ray attenuation that is measured in CT imaging. By using appropriately calibrated images we proposed a method that could homogenise the mineral density as estimated from CT images over a spatial repartition of the bone geometry [9—11]. This way, from a single CT exam, we are able to derive the geometry and the mineral density distribution over it, and from this derive the elastic properties in every point of the bone [11—13].

Loading conditions

The definition of the loading conditions depends on the pur- pose of the model. If the model is used within a validation study, the loading conditions the model simulates must be as close as possible to those imposed in the controlled experimental against which we compute the predictive accuracy of the model. Any difference between the experimental and the modelled loading conditions would appear as an inaccuracy of the predicting model.

If on the contrary we aim to predict the risk of fracture of a patient, we need to simulate, as well as possible the loading conditions that are commonly involved in this type of fractures. Thus, the definition of the loading conditions varies widely depending on the specific study: in the follow- ing we will provide more details for each clinical application we describe.

Model generation

The deformation of a solid body (continuum) with known elastic properties subjected to known loading conditions can be expressed in mathematical form using the theory of elasticity. The resulting equations are too complex to be solved, but we can find an approximate solution using a numerical method known as finite element method. Over the years various research groups developed reliable methods to transform a CT exam into one of these models [14], [15]. More recently, considerable efforts have been made to automate such model generation [16—18].

Accuracy of bone strength predictions

Bone fracture due to overloading can occur at any anatomical site. Those associated to a reduced biomechanical competence (fragility fractures) occur most commonly at wrist, followed by the ankle, spine and hip. The hip fracture is the one involving the most severe effects, and thus it is the most studied; here below we provide quantifications of accuracy for such fracture.

The standard of care accepted in most countries uses as predictor of the risk of hip fracture the areal bone mineral

density (aBMD) at the hip region using dual X-ray absorptiometry (DXA), hereinafter called DXA-aBMD. Any comparison in term of predictive accuracy should be made with this standard of care. Similarly, hereinafter we will refer to Finite Element model generated form Quantitative CT data as QCT- FE.

QCT-FE predicts strength by first predicting the biomechanical deformation induced in the bone tissue by the loading conditions. So, a first validation must be done against measured deformations. In a study involving over 600 deformation measurements (done using very reliable sensors called strain gauges) on cadaver bones loaded both physiologically and as during a fall on a side, an error of only 7% (root mean squared error normalised by the maximum mea- sured deformation) was reported [19]. DXA-aBMD does not predict strains, so a comparison here is meaningless.

The second step is to validate the accuracy of QCT- FE models in predicting bone strength, when compared to DXA-aBMD. Since the most common loading scenario for hip fracture is the fall on a side, most validation studies are conducted on human cadaver bone subjected to a loading conditions mimicking the side fall. In the literature there is no consensus of the best way to represent the average error: here we will use for the QCT-FE the Standard Error of the Estimate of the linear regression between measured and predicted values, normalised by the average measured strength (%SEE). Since aBMD measurements are only indi- rect predictors, the error metric most comparable to the %SEE used for QCT-FE models is probably the standard error of the Regression (%SER) between the measured strength and measured aBMD, again normalised by the average mea- sured strength. Looking at five large studies [20—24], the average error of DXA-aBMD as predictor of femoral strength, as measured by %SER over 300 femurs, was on average 22% (range 19—23%). For QCT-FE, when the results of four studies published in the last seven years are considered that use comparable modelling techniques [25—27], [24] and have their results reported in terms of %SEE, we find that they all report an error between 15% and 16%. This

is an impressive consistency, considering these studies were done in four different labs, using different experimental setup and modelling techniques. So, when validated *ex vivo*, QCT-FE is on average 7% more accurate than DXA-aBMD in predicting femoral strength under side fall loading conditions.

The third and last validation step is to check whether this greater accuracy found *ex vivo* does translate into a higher accuracy of QCT-FE in predicting the risk of hip fracture in the clinical practice. The problem is complex, as the prevalence of hip fractures in the general population is low, and the absolute risk of fracture is typically evaluated over 10 years. So, a true prediction accuracy is very difficult to evaluate with an observational study. A simpler approach is to consider the *stratification accuracy*. This is computed considering a group of patients, some who at the time of enrollment already had a hip fracture in the last few days, and some who at the same time did not. It is possible to select the non-fractured subjects to be pair-matched to each of the fractured ones, for gender, age, weight, height, degree of osteoporosis, etc. At the time of enrollment, the two predictors to be compared are both determined, and they are compared in term of their ability to correctly sep- arate the fractured from the non-fractured patients.

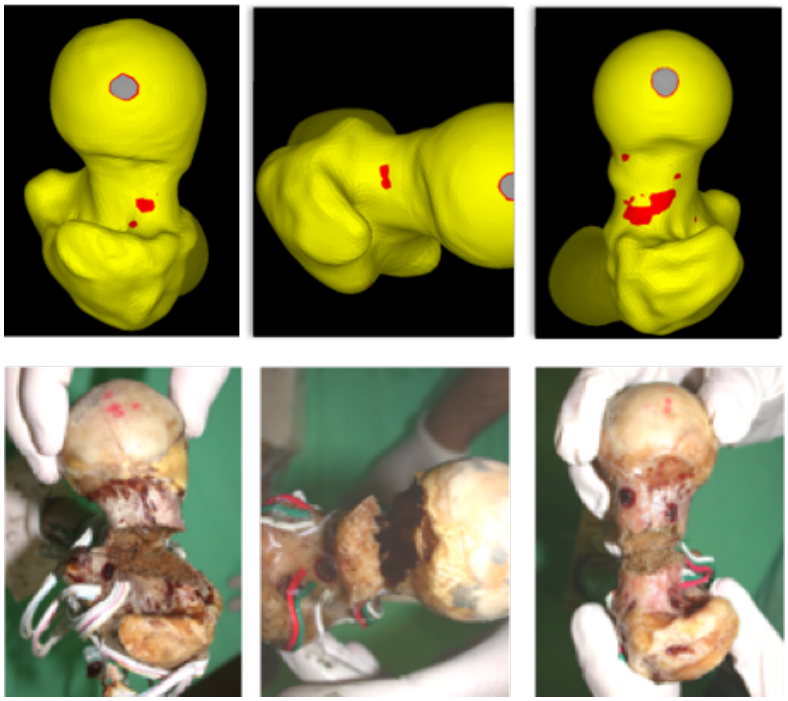

Figure 1: Investigation of fracture of a proximal femur. QCT-FE models (above) can accurately predict the point of fracture initiation as observed experimentally on cadaver specimens (below). (Reproduced with permission. Copyright © 2011 VPHOP consortium.)

One of these cohorts, referred to as the Sheffield Cohort, is formed by postmenopausal women (55 to 89 years old), 50 cases of fragility hip fracture and 50 cases of controls (no fractures), pair-matched by age, weight, and height [28]. On this cohort the stratification accuracy of QCT-FE, measured as the Area Under the ROC curve (AUC), was found to be 0.82, while that of aBMD was 0.75. Thus, QCT-FE could separate in this cohort non-fractured and fractured cases with an accuracy that is seven percentage points better than DXA-aBMD [29] (Fig. 1).

Use of QCT-FE in clinical research

On the basis of the results summarised in the previous sections, QCT-FE can predict whole bone strength as measured on cadaver bones with an accuracy around 85%, while DXA-aBMD shows an accuracy of only 77%—78%, 7 points less. On the Sheffield Cohort QCT-FE strength shows a stratification accuracy of 82%, DXA-aBMD only 75%.

Thus, any time it is clinically justified to perform a clini- cal CT, QCT-FE can provide a fairly accurate estimate of the whole bone biomechanical strength. This has enabled the use of this method in a number of clinical research studies. Here below are provided some examples:

• one of the first application was in a study where the femur of a four-year-old child affected by a Ewing's sarcoma was reconstructed using a massive bone allograft in conjunction with a vascularized fibula autograft. Using QCT-FE models generated from CT exams performed as part of the oncology routine controls it was possible to follow- up how the biomechanical strength of the reconstructed femur had changed 33 months after the operation [30].

• roughly 5% of all hip fractures cannot be positively associated to a fall. It remains debated in the literature whether this is a reporting failure, or if it is actually possible to experience a spontaneous hip fracture, a fracture that occurs during normal daily activities, not because of a fall. Using the QCT-FE technique we were able to explore this question, and propose that it is possible for spontaneous hip fractures to occur but only when a sever osteoporosis is associated to severely degrade neuromuscular control, which overload abnormally the hip during normal walking [31].

• it is very difficult to decide when a long bone fracture in an infant may be associated to physical abuse. One of the reasons is that we know very little about the forces required to fracture an infant bone; bone strength studies are done on cadavers, and infant bodies

are very rarely donated to such programs. Offiah and co-workers were able to collect a significant number of post-mortem CT scans through a program run at the Sheffield Children's Hospital. Using QCT-FE it was possible to use these CT scans to estimate the strength of infant bones at various ages [32], [33].

- subject-specific QCT-FE models were used to investi- gate the biomechanical properties in terms of stress at adjacent segments using robot-assisted pedicle screw insertion technique when compared to free-hand technique [34].

- subject-specific QCT-FE models, in combination with surgical simulation, were used to provide a stratification criterion between cementless and cemented total hip replacement [35].

Use of QCT-FE in clinical trials

Clinical trials of antiresorptive drugs are particularly challenging: the primary endpoint, bone fractures occur rel- atively rarely, and the observational time frame must be at least five years. Thus, it is commonly accepted as the use of a biomarker as a surrogate of such long-term clinical end- point: the most common is DXA-aBMD, but some studies now use instead bone strength predicted with QCT-FE.
When the stratification accuracy of QCT-FE models as measured on the Sheffield cohort was used to estimate the benefit we could expect in clinical trials of new drugs where bone strength is a clinical endpoint, a clear benefit emerged in comparison to DXA-aBMD, with reduction of the number of patients to be enrolled of 50% or better [29]. This represents a strong recommendation toward the use of QCT-FE to quan- tify bone strength in clinical trials where this information is used as a predictive biomarker of the bone fracture clini- cal endpoint. Here are some recent examples where QCT-FE was used in clinical trials of new treatments:

- a first obvious use is in clinical trials of new drugs aimed to reduce the risk of bone fracture by slowing down or even possibly reversing the progressive loss of bone strength. In the FREEDOM multicentric clinical trial, QCT-FE was used to confirm the effect of a new drug, Denosumab, when compared to placebo [36,37];

- ageing may cause in men a decrease of serum testosterone concentrations, which is believed to cause a decreased bone mineral density (BMD), and increased risk of frac- ture. In a placebo-controlled, double-blind trial on 211 men 65 years or older, QCT-FE was used to estimate bone strength, which was treated as a biomarker predictive of the

risk of fracture [41].

Use of QCT-FE in the clinical practice

The only routine use for QCT-FE which has been explored in term of cost-benefit is that of prognostic biomarker in the treatment planning of primary osteoporosis [29]. Here the analysis concluded that the method could become cost- effective, when compared to DXA-aBMD, only when it was used on a subset of "difficult" cases, and when the price- point for a QCT-FE was sufficiently low (US$ 100). This study, based on the UK healthcare costs, substantially confirmed the findings of another similar study published just a few months before and based on the USA costs [38].

However, one limit of both these studies was that they focused on the treat/no-treat decision, where the treat option for a first line therapy, bisphosphonates, is now relatively cheap. A similar analysis, if done for the decision between first line and second line treatments such as RANKL inhibitors (Denosumab), oestrogen replacement or selective oestrogen receptor modulators, or recombinant human parathyroid hormone (teriparatide), may come to different conclusions.

A second clinical use of QCT-FE is in the assessment of the risk of hip or vertebral fracture in patients at general risk who were examined with a CT for other medical reasons [39]. The scenario is being pursued commercially by a USA- based company, O. N. Diagnostics Inc[1].

A third scenario of clinical use is QCT-FE to predict the risk of bone fracture in patients with a major bone metastasis. Such lesions can be treated with radiotherapy or with a prophylactic surgical stabilisation; the first is preferable if the risk of fracture is low, otherwise the second is usually recommended. An accurate prediction of the risk of fracture could help to better stratify these patients by treatment. A recent study suggests that 39% of the patients with bone metastases that undergo prophylactic stabilisation may not be at risk of bone fracture [40]. Another suggests that QCT- FE strength was able to separate with excellent accuracy the patients with high-risk lesions form those with low-risk lesions [41].

Discussion

From this brief review of some of the recent literature, we can conclude that it is possible to predict with excel- lent accuracy the biomechanical strength of bones using finite element models informed by Quantitative Computer Tomography. These patient-specific models

are now being used for clinical research, to improve clinical trials of new treatments, and in a few cases also in the routine clinical practice.

The simplicity, robustness, and reliability of this patient- specific modelling method open new scenarios in the context of in silico trials, where virtual patient cohorts can be used to estimate the efficacy of new physical, environmental or pharmaceutical interventions [42]. The work being done in the STriTuVaD project, where we are using virtual cohorts to reduce, refine and partially replace clinical trials of new therapeutic vaccines for tuberculosis, could be easily trans- lated also to this application.

QCT-FE technologies represent an excellent example of early adoption of in silico medicine and in silico trials technologies in the clinical domain.

CONFLICT OF INTEREST

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